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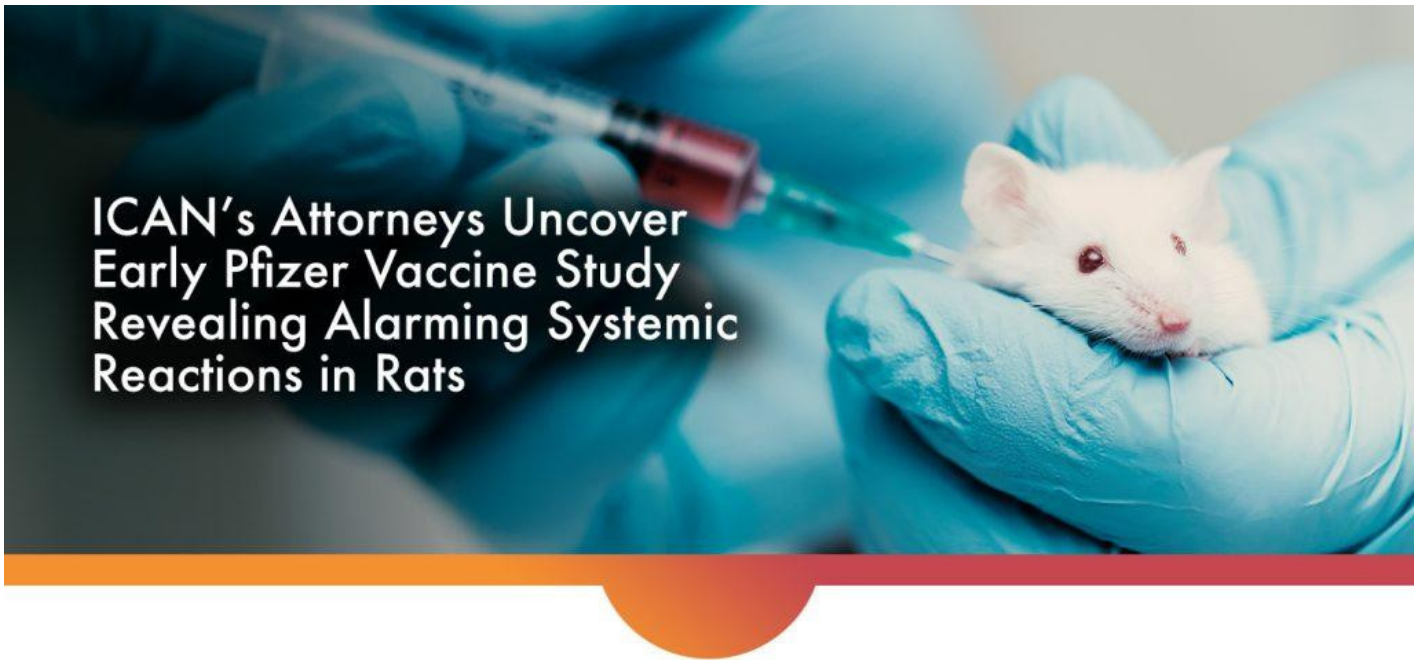
ICAN'S ATTORNEYS UNCOVER EARLY PFIZER VACCINE STUDY REVEALING ALARMING SYSTEMIC REACTIONS IN RATS

ICAN | LEGAL UPDATE



This month, ICAN's attorneys reviewed a startling 2,237-page report from June 2020 (amended in September 2020) that Pfizer submitted to the FDA concerning its mRNA COVID-19 vaccine.

The study looked at the toxicity of Pfizer's vaccine using four different doses (including the one eventually authorized for emergency use, BNT162b2) and involved 255 rats (219 received vaccine, 36 received control) for a test period of 10 to 17 days with "3 additional weeks for the animals scheduled for the recovery period."

One would imagine that, since the vaccine was authorized, approved, and injected into millions, the rats did not experience any negative health effects. Sadly, that is not the case.

While the Pfizer claims in the report that the rats tolerated the vaccines “without evidence of systemic toxicity,” its detailed findings indicate that was anything but the truth, as the following issues in major organs groups were observed:

- Enlarged spleens
- Enlarged adrenal glands
- Enlarged lymph nodes
- Kidney and liver congestion
- Increased fibrinogen concentration

All of these issues clearly show effects beyond the injection site. Of particular concern is the increased fibrinogen concentration; fibrinogen is made in your liver and helps your blood clot. Increased fibrinogen is associated with blood clotting, heart disease, blood vessel dysfunction, and stroke. These issues were also seen with the dose level that was eventually licensed.

With regard to deaths, the report indicated that “[n]o test item-related deaths were noted for any treatment” and that “no premature deaths occurred and no premature sacrifice was necessary.” That seems reassuring, right? It only took slightly closer reading to discover, however, **that two rats did die** during the study (about 1% of those injected with vaccine), but, predictably, the Pfizer paid researchers, despite being unable to determine a clear cause of death, simply **assumed** that the deaths were caused by stress from blood draws and therefore were not caused by the vaccines (despite the fact that one of the dead rats had an enlarged spleen, enlarged adrenal glands, and an enlarged iliac lymph node)!

Given the short six-week study duration, it’s not possible for the researchers to have ascertained the long-term effects of the vaccines. Nevertheless, throughout the report, they conclude that all adverse effects experienced by the rats were “reversed” and “resolved” by the end of the recovery period.

You can read the entire report and the rest of the recent production here.

https://icandecide.org/press-release/icans-attorneys-uncover-early-pfizer-vaccine-study-revealing-alarming-systemic-reactions-in-rats/

COMMENTARY

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Aβ peptide and fibrinogen weave a web of destruction in cerebral amyloid angiopathy

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Alzheimer's disease (AD) is characterized by disruption of the normal brain architecture which is driven by the formation of two pathological structures, including senile plaques and neurofibrillary tangles. The amyloid-β (Aβ) peptide, derived from Aβ precursor protein (AβPP), is the major component of senile plaques in the brain and cerebrovasculature. Substantial evidence has demonstrated that the Aβ peptide is a major contributor to the

neurodegenerative process, acting through local neurotoxic and inflammatory processes (1). Cerebral amyloid angiopathy (CAA) is a common pathological feature of AD and results from Aβ deposits in and around cerebral blood vessels that are believed to mediate disruption of the brain vasculature. Importantly, Aβ does not act alone, but rather it exerts pathophysiological effects by forming complexes with the blood-clotting protein fibrinogen (2). Although an association between Aβ and fibrinogen has been appreciated for over a decade, the molecular features of this interaction as well as the precise downstream consequences have been a significant knowledge gap.

CAA is routinely observed in spontaneous AD that afflicts individuals late in adulthood. However, there are familial forms of CAA that are appreciated earlier in life and lead to exacerbated cerebrovascular disease. Indeed, a subset of inherited Aβ mutations specifically promote more pronounced vascular Aβ deposits, resulting in a condition termed hereditary cerebral amyloid angiopathy (HCAA). To better characterize molecular mechanisms mediating CAA, Cajamarca et al. (3) have analyzed Aβ deposition and the association with fibrinogen in the context of the most common forms of HCAA, including Aβ Dutch (E22Q) and Iowa (D23N).

The hypothesis that Aβ and fibrinogen form a pathological nexus extends back to the first observations that fibrin(ogen) accumulates and colocalizes with Aβ plaques as observed in postmortem brain tissues of AD patients (2, 4). A direct functional contribution of fibrinogen to AD pathogenesis has been shown using mouse models. In transgenic models of AD, genetic and pharmacological treatments that exacerbate fibrin deposition resulted in more severe pathology (2). In complementary loss-function studies, genetic heterozygous deletion of the fibrinogen Aα-chain gene or pharmacological depletion of circulating fibrinogen exhibited reduced neuroinflammation and microvascular damage. Intriguingly, fibrinogen depletion in these studies was only 50 to 75%, suggesting that the degree of vascular damage was highly sensitive to fibrinogen levels (2). A separate study specifically documented a strong positive correlation between the amount of fibrin(ogen) deposition in the AD brain and the extent of neuronal and cerebrovascular pathology in both mouse models and patients with AD (5). Collectively, these findings established the basis that genetic or biochemical determinants of Aβ–fibrinogen interactions or deposition function as potent modifiers of CAA and AD.

The basis of the mechanism linking Aβ and fibrinogen to CAA and AD pathology is the finding that these two proteins directly interact (6). An interesting point of commonality to consider in evaluating the association is that both proteins undergo significant and parallel structural changes. Both proteins are initially formed as soluble monomeric factors, both undergo proteolytic processing, and subsequently both spontaneously form large polymer structures.

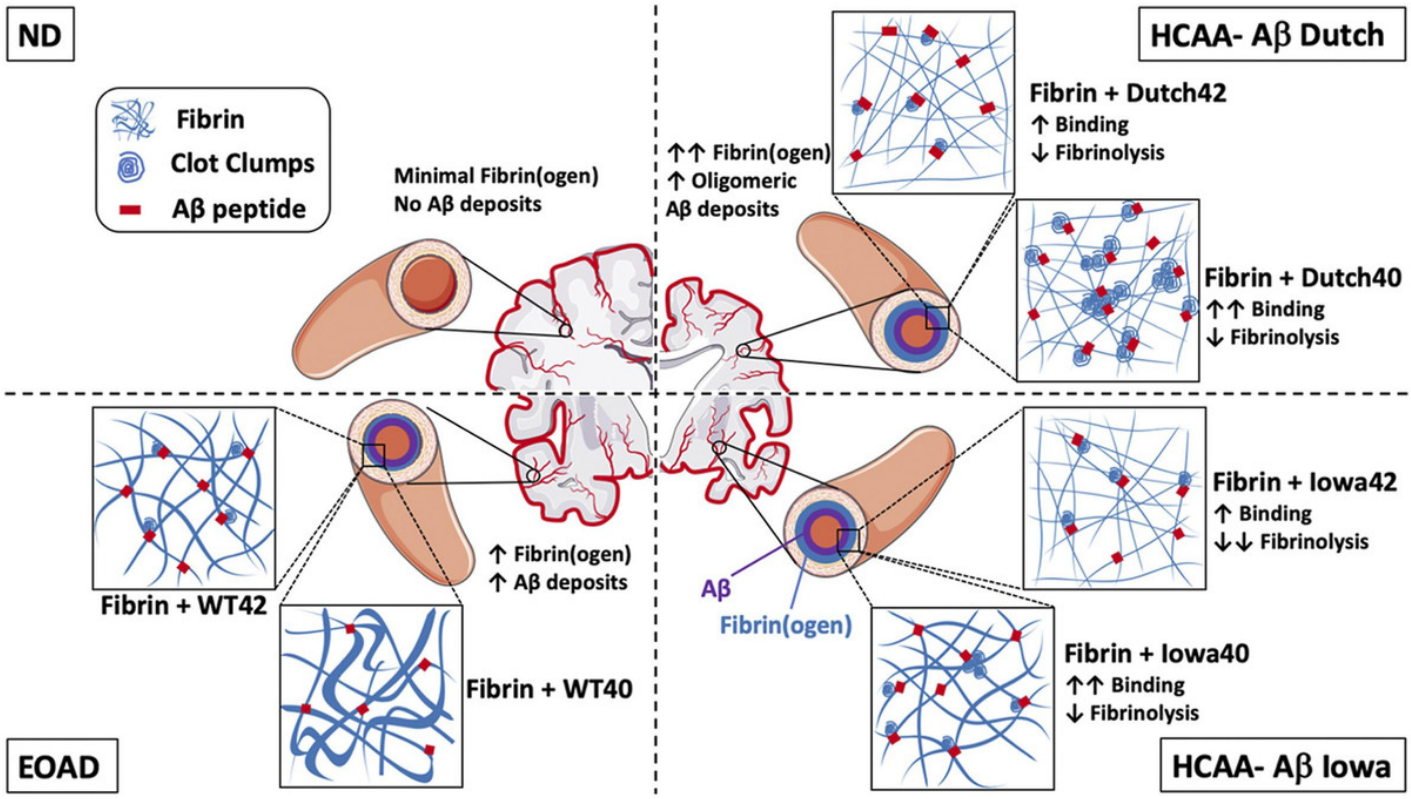
AβPP is processed in a series of proteolytic events by β-secretase and subsequently an intramembranous γ-secretase complex that ultimately produces the amyloidogenic Aβ peptides (e.g., 1–40, 1–42) that can self-assemble into a fibrillar structure (reviewed in ref. 7). Similarly, fibrinogen is a soluble monomer that is cleaved by the central coagulation protease thrombin into fibrin that self-assembles into fibrin polymer. Fibrin is the primary structural component of the blood clot that dictates biophysical and biochemical properties of the clot. Fibrin is essential for hemostasis and vascular repair following injury but also exerts deleterious effects in the context of thrombosis, occlusive pathological clots. Abnormalities in fibrin structure and/or clearance are linked to bleeding disorders and numerous thrombotic pathologies (e.g., myocardial infarction, ischemic stroke, and venous thromboembolism) (reviewed in ref. 8). Notably, fibrin polymers also form in the extravascular space following tissue injury, and extravascular fibrin deposits have been shown to promote inflammatory diseases in a number of contexts (e.g., arthritis, colitis, obesity, and neuromuscular disease) (9–13). Thus, it follows that modifiers of fibrin structure have the potential to exert a significant impact on disease progression whether the fibrin is formed within or outside of vessels.

The impact of Aβ peptide/fibrinogen interactions is multifactorial. In vitro studies of fibrin clot formation in the presence of Aβ1–42 peptide revealed changes in both the structure of the fibrin network and susceptibility to degradation by the fibrinolytic enzyme plasmin. Fibrin/Aβ1–42 clots were shown to form thinner fibrils with an increase in network density but that also contained tight aggregates composed of both fibrin and fibrillar Aβ. Additionally, these altered fibrin/Aβ1–42 structures were shown to be resistant to plasmin-mediated degradation (14) that was due to both the change in the network structure and Aβ-mediated inhibition of fibrin(ogen)–plasminogen binding (15). That these Aβ/fibrin(ogen) networks and aggregates are a source of pathologic activity in CAA is supported by studies documenting their presence with brain tissue of AD patients within vessels, adjacent to vessels, and within the brain parenchyma (2, 5, 14). In addition, selective disruption of the Aβ/fibrin(ogen) interaction using a pharmacological inhibitor in a mouse model of AD significantly inhibited vessel occlusion, reduced vascular amyloid deposition and microgliosis, and limited cognitive impairment (16).

The current study takes advantage of known HCAA-type mutations to significantly enhance the understanding of the Aβ-peptide/fibrinogen interaction on several fronts (Fig. 1). The oligomeric forms of the Aβ-peptide Dutch and Iowa mutants showed significantly increased binding to fibrinogen that translated to corresponding profound alterations in fibrin clot structure. These findings highlight the functional importance of Aβ residues 22–23 in fibrinogen binding. Intriguingly, the binding of Aβ-Dutch and Aβ-Iowa on fibrin were independent of proto/fibril length, suggesting that the downstream effects of Aβ on fibrin clot structure are dictated by affinity and/or the structural nature of the protein–protein interface. Effects exhibited by Aβ-Dutch and Aβ-Iowa, although similar, were not identical and the degree of impact depended on whether the mutations were in the context of Aβ1–40 or Aβ1–42. Incubation with either Aβ-Dutch or Aβ-Iowa produced more pronounced changes in fibrin with

thinner fibers, a denser network, and more numerous clot “clumps” relative to incubation with native Aβ. However, qualitative and quantitative differences were observed. For example, Aβ Dutch1–40 mediated the most profound changes, resulting in fibers of the smallest diameter and producing the greatest number and size of clumps or aggregates, an intriguing finding as Aβ1–40, not Aβ1–42, is the prominent component of Aβ deposits in CAA (17). As expected, based on the increased binding affinity and greater impact on fibrin clot structure, clots formed with mutant Aβ1–40 or Aβ1–42 demonstrated an enhanced resistance to clot lysis over clots formed with native Aβ1–40 or Aβ1–42.

Fig. 1.



The Aβ variants Dutch and Iowa linked to HCAA display increased binding to the coagulation protein fibrinogen that results in profound perturbation of fibrin networks and a significant reduction in fibrinolysis relative to native Aβ associated with EOAD. The deposition of Aβ /fibrin(ogen) is significantly elevated within and around the cerebrovasculature in HCAA patients. ND = nondementia. OPEN IN VIEWER

> To better characterize molecular mechanisms mediating CAA, Cajamarca et al. have analyzed Aβ deposition and the association with fibrinogen in the context of the most common forms of HCAA, including Aβ Dutch (E22Q) and Iowa (D23N).

Consistent with the enhanced binding properties, profound alteration in clot formation, and resistance to fibrinolysis driven by the HCAA Aβ-peptides, Cajamarca et al. (3) also document significantly elevated levels of colocalized fibrin(ogen)/Aβ deposits in brain tissue from HCAA Dutch patients relative to early-onset AD (EOAD) patients. These deposits were found within

intravascular and extravascular (parenchymal) areas of CAA pathology. The deposits were particularly prominent in and around the cerebral vessels of HCAA patients. Intriguingly, it was also documented that the Aβ within CAA plaques was present in the oligomeric or fibrillar form. The authors document fibrillar Aβ did not increase binding to fibrinogen, but it clearly impacted fibrin network structure. An open question not investigated by the present work is whether fibrinogen or fibrin impacts the oligomerization of native or mutant Aβ molecules.

The present study builds on a growing body of evidence that Aβ and fibrinogen form a pathologically functional unit in AD by suggesting that the structural composition of Aβ/fibrin(ogen) complexes is likely a determinant of the contribution of those molecules to disease progression and severity. Indeed, both molecules may be present as monomers or fibrillar polymers and the relative amount of each species could be quite heterogenous. Recent analyses on the contribution of fibrin(ogen) to liver injury have suggested that not only are deposits of fibrinogen, fibrin, and cross-linked fibrin present within injured zones but that each molecule exerts unique effects on cells in the microenvironment to influence distinct aspects of tissue injury, remodeling, and repair (18). It is possible that similar unique fibrin(ogen)-driven contributions could be made in AD. In this regard, a compelling candidate for deeper investigation that is both a modifier of fibrin structure and has been implicated in CAA and AD is the coagulation transglutaminase factor (F)XIII. Notably, FXIII is activated by thrombin and contributes to hemostasis and thrombosis by cross-linking fibrin fibrils to stabilize the clot structure. However, FXIII has also been shown to colocalize with Aβ in CAA, to cross-link Aβ into oligomers, and to cross-link Aβ to fibrin and other coagulation proteins (19, 20). Defining the role of different fibrin(ogen) species in AD as well as the precise interplay of Aβ, fibrinogen, and FXIII in dictating Aβ/fibrin(ogen) structure and pathological function will be the next step in defining the pathogenesis of this debilitating disease.

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